PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Rajagopalan, et al.
Serial No.:	09/898,809
Filed:	July 3, 2001
Group Art Unit:	1624
Confirmation No:	5120
Examiner:	McKenzie
Title:	**DYE-SULFENATES FOR DUAL PHOTOTHERAPY**
Our Ref. No.:	MRD-63

Cincinnati, Ohio 45202 August 20, 2004

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22311450

DECLARATION OF RAGHAVAN RAJAGOPALAN PURSUANT TO 37 C.F.R. §1.132

Sir:

I, RAGHAVAN RAJAGOPALAN, declare as follows:

1. I am a named inventor in the above-identified patent application.

2. I hold a Ph.D. in Organic Chemistry from Columbia University. I have 22 years of experience in the synthesis and use of compounds for medical diagnosis and therapy, which is the subject of the application. I have read the May 21, 2004 Office Action and understand the position of the Examiner.

3. With respect to enablement of the inventive compound, I respectfully disagree with the Examiner. As I have previously declared, it is my opinion that one skilled in the art would recognize that the targeting moiety is selected based upon the target site. Stated differently, one chooses the targeting moiety based upon where one seeks to locate the inventive dye in the body. The targeting moiety is thus a binding partner for the desired target so that, upon binding to the target, the dye is localized at that site. In my opinion, the application fully discloses the broad classes encompassed by E, enabling one skilled in the art to select the identity of E based upon the target site.

4. I further disagree with the Examiner that I have made no arguments against the enablement rejection but simply assert that they are enabled for making the inventive compounds. My previous Declaration, paragraphs 10-17, argued against this rejection with (a) a functionally defined targeting moiety; (b) its selection by one skilled in the art; (c) its binding site; and (d) how one skilled in the art would practice the invention without undue experimentation, with specific examples for somatostatin, bombesin, and neurotensin receptor binding sites, and specific examples for cholecystekinin, dihyroxyindolecarboxylic acid, and integrin targeting.

5. I respectfully assert that the claims require a method for performing a phototherapeutic procedure using the inventive dye-sulfenates. The claims do not require determining the binding affinity of the inventive compounds to a

particular receptor with a particular affinity, nor do the claims require synthesis of the compound.

6. Further, it is my opinion that one skilled in the art would be able to practice the invention without undue experimentation, as demonstrated in the following step by step process, which I assert that one skilled in the art would follow without undue experimentation.

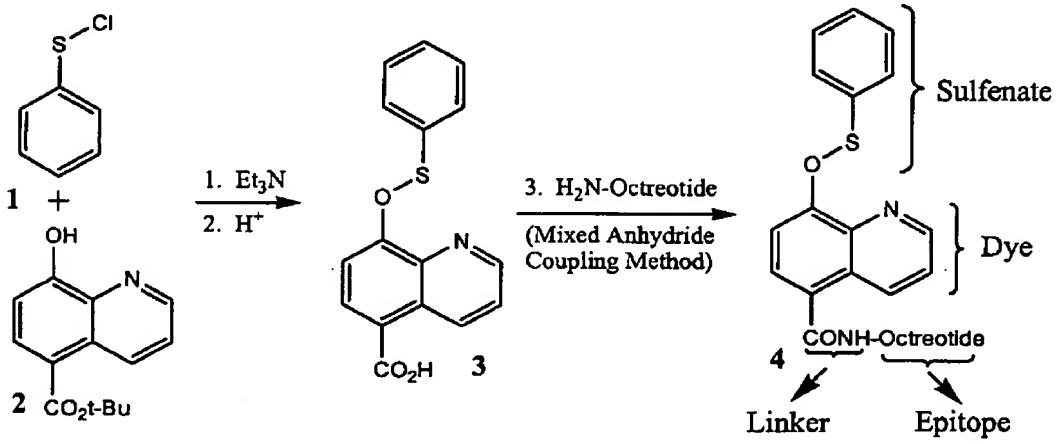
7. The first step selects the targeting group. The targeting group can be selected in a number of ways based upon the patient's diagnosis, for example, conducing a literature search, consulting with a clinician, or knowing about the tissue that is to be targeted. Tumors overexpress a plethora of receptors; the types of molecules (both macromolecules and small molecules) that bind to these receptors are widely known. For example, malignant tumors of the colon express a high level of receptors (referred to as ST receptors) that bind to a polypeptide called heat sensitive bacterioendotoxin, as well as the well-known carcinoembryonic antigen (CEA). Anti-CEA antibodies have been known for over two decades and radioiodinated anti-CEA conjugate is in commercial use as an imaging agent in cancer patients for diagnosing or monitoring. Likewise, a polypeptide binding to ST receptors has been radiolabeled and has been demonstrated to bind to these receptors. Both of these agents have the requisite coupling group (e.g., an amino, carboxyl, hydroxyl, etc.) to link them to an effector moiety (e.g. radionuclides, fluorescent molecules, photosensitizers,

etc.). Hence, selecting a binding molecule that possesses a coupling group is not undue experimentation; indeed, most of the bioactive molecules intrinsically contain many functional groups that enable the attachment of these molecules to an effector. Although the affinity of the binding molecule is not part of the claimed method, if desired, it may be determined by competition binding assay using known cell lines that express various receptors. As only one example, it is known to one skilled in the art that the pancreatic tumor cell lines CA20948 and AR42-J express somatostatin-2 (SST-2) and bombesin receptors, respectively. Compounds are selected that have a desired receptor specificity, as can be determined, for example, by IC_{50} values (e.g., an IC_{50} < 100 nM indicates high specificity). IC_{50} values may be calculated using a software program (e.g., GraFit, Erithacus, UK). As only one specific example, one skilled in the art would select octreotide, which is a somatostatin receptor binding molecule for receptors found in neuroendocrine tumors, that has a free N-terminal amino group by which it attaches to the claimed formula by an amide bond.

8. The next step prepares the sulfenate derivative bearing a complementary coupling group (amino, carboxyl, hydroxyl, etc.). For example, an aromatic sulfenate derivative of the present invention can be readily prepared by reacting phenylsuflenyl chloride with various bifunctional dyes bearing a hydroxyl group to provide the requisite sulfenate moiety. This is disclosed in the specification at least at page 15, lines 3-13.

9. The final step couples the targeting group with the sulfenate using routine methods of bioconjugate chemistry. For example, if the sulfenate compounds contain a carboxyl group, coupling with targeting molecules bearing an amino functionality can be accomplished in solution phase in any number of methods, including direct coupling using carbodiimides, a mixed anhydride procedure, or through an N-succinimido active ester intermediate. If necessary, conjugates may also be prepared by standard automated solid-phase methods with a commercial peptide synthesizer, where the last coupling involves the sulfenate derivative.

10. The following schematic shows these steps for a specific embodiment of the invention. Every component of the ensemble of the claimed formula is prepared by routine methods known to one skilled in the art and not requiring undue experimentation, as I have described.



I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

August 19, 2004
Date

Raghavan Rajagopalan
Raghavan Rajagopalan, Ph.D.